

Epidemiology and risk factors of preeclampsia; an overview of observational studies

Uzma Shamsi*, Sarah Saleem and Noureen Nishter

Department of Community Health Sciences, Aga Khan University Hospital, Stadium Road, Karachi-74800, Pakistan

Abstract: *Objective:* To identify and compile a list of important epidemiological risk factors of preeclampsia among pregnant women from observational studies. *Methods:* Review of published case control and cohort studies on risk factors of Preeclampsia (PE) by literature search from 1976 -2010 was conducted. 108 studies were selected using search engines of PubMed and Google Scholar. *Findings:* Most of the studies were case control studies. The factors identified most often were women with a previous history of preeclampsia, pre-existing diabetes, multiple (twin) pregnancy, nulliparity, family history, raised blood pressure (diastolic ≥ 80 mm Hg) at booking, raised body mass index before pregnancy, or increasing maternal age ≥ 40 . In some individual studies the risk is also increased with an interval of 10 years or more since a previous pregnancy, autoimmune disease, renal disease and chronic hypertension. *Conclusions:* These factors and the underlying evidence base can be used to assess risk at booking so that a suitable surveillance routine to detect preeclampsia can be planned for the rest of the pregnancy.

Keywords: Preeclampsia, proteinuria, diabetes mellitus, gestational diabetes, risk factors for PE

Introduction

Preeclampsia (PE) is a pregnancy-specific condition that increases maternal and infant mortality and morbidity. It is diagnosed by new-onset increased blood pressure and proteinuria during second or third trimester of gestation [1]; Key features of the preeclampsia category include a cut-off blood pressure of 140/90 mm Hg or higher and absolute requirement of proteinuria. Abnormal placentation related to immune mechanisms and maladaptation of the placenta may be the first step in the etiology and development PE [2-3]. It is obvious that a single mechanism responsible for the syndrome preeclampsia does not exist. Instead, several mechanisms can act together and even multiply each other [4].

Preeclampsia is a serious and poorly understood complication of pregnancy, which can progress to eclampsia and maternal death, is an important cause of maternal mortality in developing countries [5]. Preeclampsia is a major cause of maternal mortality (15-20% in developed countries) and morbidities (acute and long-term), perinatal deaths, preterm birth, and intrauterine growth restriction [6]. Preeclampsia occurs in an

estimated one in 20 pregnancies. It can develop into eclampsia, or convulsive fits, which account for up to 10 percent of maternal deaths. From another public health perspective, it is alarming that the rate of preeclampsia has increased in worldwide especially in developed countries by 40% between 1990 and 1999 due to an increase in number of older mothers and multiple births, conditions known to increase the risk of preeclampsia [7]

An estimated 50,000 women worldwide die annually from preeclampsia. The incidence of preeclampsia is 2-10%, depending on the population studied and definitions of preeclampsia [8]. The incidence was 2.8% reported from a study in Israel [9], 5.8% reported from Scotland [10], 14.1% reported from Australia [11] and 5% reported from Seattle. It occurs in 5 to 8 per cent of pregnant women worldwide and can cause the most serious problems for the mother and the child [12].

Despite a steady reduction in maternal mortality from the disorder in more developed countries, it remains one of the most common

reasons for a woman to die during pregnancy [13]. In developed countries, where maternal mortality attributable to preeclampsia has been reduced, the condition primarily affects fetal well-being through intrauterine growth retardation, preterm birth, low birth weight, and perinatal death [14-16].

The study of risk factors and the underlying evidence base can be used to assess risk at antenatal booking so that a suitable surveillance routine to detect preeclampsia can be planned for the rest of the pregnancy. The knowledge of the most important risk factors in the population could be useful for the clinicians to pre-detect the patient who will develop preeclampsia. In order to increase PE screening, it is imperative to develop a model that can predict individual PE risk.

Material and Methods

We searched PubMed and Google Scholar for selecting studies with a cohort or case-control design that identified preeclampsia risk factors. Articles were selected using predetermined criteria and reviewed in depth in line with the search objective.

Inclusion criteria: Overall selection criteria for this literature review were set in line with the study objective of PE risk factors among women to capture important PE studies. Inclusion criteria were: Publications should be in English language and peer reviewed; studies published between 1976-2010; publications involving case control and cohort studies mostly and publications should have a focus on risk factors for PE.

This review was conducted in two stages:

- Stage 1: review of the titles/abstracts (first level review).
- Stage 2: review of complete articles that fulfill the selection criteria (second level review).

The key words & MeSH terms used for the search were preeclampsia, risk factors for preeclampsia in titles and abstracts. Articles that defined biological markers as risk factors were excluded as it cannot be predictors of a model for promoting early antenatal screening tests.

Findings

Preeclampsia is a common condition, but the etiology remains unknown. Despite numerous basic, clinical, and epidemiologic studies that have been conducted over the past half-century, knowledge of the etiology and pathogenesis of preeclampsia remains elusive. Preeclampsia is probably the common final syndrome resulting from heterogeneous causes. Preeclampsia may be placental in origin and may also be influenced by maternal factors such as obesity, diabetes [17]. Preeclampsia appears to have a genetic component through the father as well as mother [18]. Currently, women who are at increased risk for preeclampsia are identified on the basis of epidemiologic factors [19].

The known risk factors are extremes of age, poor socioeconomic status, smoking, high body mass index, family history of preeclampsia, history of preeclampsia in previous pregnancy, parity and type of pregnancy (single or multiple), family history of diabetes mellitus and hypertension [20-32]. A first pregnancy, diabetes mellitus, preexisting hypertension or previous preeclampsia, multiple gestation, and higher body-mass index are among the recognized risk factors for the disorder, but they lack sensitivity and specificity. Parity is the most predictive of preeclampsia risk [33].

Risk factors of preeclampsia among Nulliparous women: Nulliparity has been confirmed as a risk factor for preeclampsia. The risk of preeclampsia was 26% in nulliparous patients versus 17% in parous subjects (relative risk and 95% confidence interval 1.5 [1.3-1.8] [32]. Pregnancy exerts a protective effect against the risk of preeclampsia which may have an immunological basis. Among nulliparous women, the risk of preeclampsia is increased with history of abortion, changed paternity and high body mass index [34]. There is definitely a genetic component, but studies of twins indicate that there is more to preeclampsia than genes alone [35]. Both the mother and the fetus contribute to the risk of pre-eclampsia, the contribution of the fetus being affected by paternal genes [36-37].

Risk factors of PE among parous women: Among parous women, significant risk factors for preeclampsia in a second pregnancy include longer birth interval, previous preterm delivery, previous small-for-gestational-age newborn, renal disease, chronic hypertension, diabetes mellitus, obesity, black race, and inadequate prenatal care. Smoking and same paternity are protective [38]. A prior birth confers a strong protective effect against Preeclampsia, whereas a prior abortion confers a weaker protective effect. Parous women who change partners in a subsequent pregnancy appear to lose the protective effect of a prior birth. Thus, the protective effect of a prior abortion operated only among women who conceived again with the same partner. An immune-based etiologic mechanism is proposed, whereby prolonged exposure to fetal antigens from a previous pregnancy protects against preeclampsia in a subsequent pregnancy with the same father [39-40].

Risk factors of PE among both nulliparous and parous women in Pakistan: Maternal Mortality is extremely high in Pakistan chiefly due to pregnancy related complications; it is estimated to be approximately 500 per 100,000 live births [41]. Risk factors for preeclampsia that may place Pakistani women at increased risk are those who have a family history of hypertension, gestational diabetes, pre-gestational diabetes and mental stress during pregnancy [42]. However, high body mass index, maternal age, urinary tract infection, use of condoms prior to index pregnancy and sociodemographic factors were not associated with higher risk of having preeclampsia among Pakistani women.

Association of PE with risk of chronic diseases: Emerging evidence of relationship of preeclampsia with long-term coronary vascular disease and some cancers makes it one of important public health problems. Because of the clear public health concerns engendered by PE and the urgency of this important health issue, there is an immense need to focus on it through research studies and review of those studies.

Maternal-specific risk factors

Maternal age (years), Maternal height (in cms) and Body mass index: There is a conflicting data on the relationship of age with preeclampsia. Some studies have reported association between

age and preeclampsia especially in elderly women above the age of 35 years, while others have shown an association of preeclampsia with younger age groups. Advancing maternal age as well as young maternal age is a risk factor for PE [20, 22-24, 35, 43-45]. Amongst the complications during pregnancy, pregnancy induced hypertension was commonest complication in elderly primigravidas [46]. A high proportion of preeclampsia cases occur in those at the extreme ends of the reproductive age [38]. Women above 40 years had twice the risk of preeclampsia, whether they were primiparous or multiparous women [47].

Shorter maternal height is associated with higher risk of preeclampsia [48]. There is evidence of strong and consistent relationship between high prepregnancy body mass index and preeclampsia [49, 50]. Studies have shown that obesity is a definitive risk factor for preeclampsia risk.

Past history of preeclampsia in multiparous women: Mothers who had preeclampsia in the first pregnancy are known to be at a substantially higher risk to develop preeclampsia in a subsequent pregnancy [51-52]. Multiparous patients with a past history of severe preeclampsia are a high risk population which should be identified early in pregnancy [27].

Maternal blood group: With respect to blood group O, A, B and Rh type, no statistically significant correlation with severe preeclampsia has been found. However in one study an increased risk of preeclampsia for mothers with blood type AB (adjusted odds ratio = 3.07; 95% confidence interval 1.48-6.36) has been found out. Although these results should be considered with caution, they support the hypothesis of a linkage mechanism involving blood group in the inheritance of susceptibility to preeclampsia [53-54].

Interval between pregnancies (in years): Some researchers have found that a long time to pregnancy is associated with preeclampsia, supporting the hypothesis that some factors delaying clinically recognized conception may

also be in a causal pathway for preeclampsia [34, 55-57]. The risk in a second or third pregnancy was directly related to the time that had elapsed since the preceding delivery, and when the interbirth interval was 10 years or more, the risk approximated that among nulliparous women. After adjustment for the presence or absence of a change of partner, maternal age, and year of delivery, the odds ratio for preeclampsia for each one-year increase in the interbirth interval was 1.12 (95%CI; 1.11 to 1.13) [58]. In a cross sectional study, women with more than 59 months between pregnancies had significantly increased risk of preeclampsia compared with women with intervals of 18-23 months [23].

Number of previous abortions: A history of abortion in nulliparous women is a protective factor against the risk of preeclampsia in the subsequent pregnancy [50, 59-60]. Multiparous women, both with and without a history of abortion, have a reduced risk of preeclampsia compared to nulliparous women with no history of abortion [50]. In another study, having a previous history of a spontaneous abortion was protective but only in multiparous women [61].

Sex of newborn: Mild preeclampsia seems to be associated with the carrying of a male fetus which may be due to increased testosterone [62, 105].

Medical history of any autoimmune disease: Women with rheumatic disease had significantly higher rates of preeclampsia and cesarean section. The relative risk of preeclampsia was particularly high in women with connective tissue disease [63].

Gestational diabetes: Gestational diabetes is associated with preeclampsia [64-66]. The rate of preeclampsia is influenced by the severity of gestational diabetes. Optimizing glucose control during pregnancy may decrease the rate of preeclampsia, even in those with a greater severity of gestational diabetes [67]. Optimizing glucose control during pregnancy may decrease the rate of preeclampsia, even in those with a greater severity of gestational diabetes [67-69]. There is accumulating evidence that preeclampsia is at least partially mediated by insulin resistance, and that individuals with preeclampsia may have clinically silent and persistent alterations in insulin resistance. However, these findings

remain controversial because other studies have not observed a higher frequency of preeclampsia in gestational diabetic women [70]. Recognized associations between correlates of insulin resistance and preeclampsia show that preeclampsia may be part of the spectrum of the insulin resistance syndrome [65].

Medical history of Diabetes mellitus: In women with pre-gestational diabetes, the rates of preeclampsia and adverse neonatal outcome increase with increased severity of diabetes [71]. The results of the study showing a relationship between preeclampsia and diabetes among Pakistani women is also consistent with other studies' findings [72]. In women with pre-gestational Type 1 diabetes, the rates of preeclampsia and adverse neonatal outcome increase with the presence of diabetes [73].

Family history of hypertension and diabetes among first blood relations: There are consistent findings of a positive association between family history of diabetes and hypertension and preeclampsia risk [74-76]. Family history of hypertension is a proxy measure for hereditary factors as well as common environmental or behavioral exposures that may underlie preeclampsia risk. Women's family history of chronic hypertension is an important and easy to acquire clinical risk marker of preeclampsia compared to the biochemical markers. The family history of hypertension questions can be used as screening tool to identify pregnant women who need closer monitoring for the signs of preeclampsia during early pregnancy.

Family history of Preeclampsia: In a primigravida, a family history of preeclampsia is associated with a fourfold increased risk of severe preeclampsia. This clinical history identifies a group who warrant close clinical surveillance during pregnancy and who may be suitable for trials of prophylactic interventions [77]. Genetic factors are important in the development of preeclampsia as well as gestational hypertension. In efforts to identify women with elevated risk of developing preeclampsia during pregnancy, a question about family

history of preeclampsia is important [22, 78]. The findings from these studies are biologically plausible for reason that epidemiological and clinical data document a close association between insulin resistance, type 2 diabetes, and hypertension [79].

Pregnancy-associated risk factors

Urinary tract infection: Some studies show a significant increase in urogenital infection in preeclamptic pregnancy. This may reflect higher rates of underlying renal disease and placental bed abnormalities occurring in preeclampsia [80]. Antepartum urinary tract infection is a risk factor for preeclampsia [24, 81-82]. Urinary tract infection or chronic sub clinical infections may cause increased maternal cytokine levels sufficient to affect vascular endothelial function, and so prime individuals for the subsequent development of preeclampsia [83]. Some data show a significant increase in urogenital infection in preeclamptic pregnancy. This may reflect higher rates of underlying renal disease and placental bed abnormalities occurring in preeclampsia [80]. Infectious agents have also been suggested to play a causal role also in atherosclerosis [84]. These studies suggest there may be a possible link between infection and preeclampsia. Urinary tract infection during pregnancy may add to the inflammatory burden of a pregnancy and trigger preeclampsia in susceptible women [85].

Fetal malformations: Preeclampsia risk increases with structural congenital anomalies, polyhydramnios, hydrops fetalis, chromosomal anomalies like downs syndrome and hydatidiform moles [86].

Partner-related risk factors: Change in partner (Primipaternity: pregnancy with new father): The term primipaternity was introduced by Robillard et al [87]. According to this theory, preeclampsia may be a problem of primipaternity rather than primigravidity. The control of placentaion may well have an immunological basis with an interaction occurring between maternal and fetal genes [15]. This could explain why women are more at risk of pre-eclampsia in their first pregnancy and why parous women who later conceive by a new partner also have an increased susceptibility to the syndrome. Many studies confirm that change of partner raises the risk for

preeclampsia in subsequent pregnancies. Multiparous women with a new partner should be approached as being primigravid women. The inter-pregnancy interval, which is strongly associated with change of partner, may confound or modify the paternal effect on preeclampsia [88]. Immune maladaptation on the fetal maternal interface could be an underlying mechanism.

Limited sperm exposure (condom use): The use of condoms, spermicides and withdrawal are associated with developing of preeclampsia in subsequent pregnancy [89]. Compared to the use of condoms, use of contraceptive methods that permit exposure to sperm viable with uterus decreased the prevalence of preeclampsia [90]. Use of condoms may contribute to as many as 60% of preeclampsia cases [91-92]. The very high incidence (24%) of preeclampsia among new paternity multiparous women was shown to be related to remarkably short period of sperm exposure preceding conception [93]. Multigravid women with a period of unprotected sexual cohabitation of longer than 6 months had a decreased risk of preeclampsia [94].

Husband's age (in years): Compared with pregnancies involving fathers aged 25 to 34, the risk of preeclampsia was 24% higher if men were 35 to 44 and 80% higher if they were 45 and older [95-97]. A possible explanation for the findings is that sperm are damaged because of genetic mutations that occur with aging or from environmental causes such as radiation, heat and pesticides. Such defects may somehow raise the risk of preeclampsia.

Exogenous factors

Smoking (risk decrease): Many studies show that cigarette smoking is associated with a lower rate of pre-eclampsia among primigravidas independently of other maternal factors. The protective effect of smoking appears to continue even after cessation of smoking [60, 98-100]. Perinatal outcomes were significantly worsened among preeclamptics who smoked [99, 101-104]. However, the harmful consequences of smoking on pregnancy outcome far outweigh

this risk reduction [98, 104]. However, some study results did not support the proposition that cigarette smoking protected women against preeclampsia.

Stress & Working women status: (Work-related psychosocial strain): Work related stress is also a risk factor for preeclampsia. Pre-eclamptic women were also more likely to work during pregnancy (adjusted OR, 2.1; 95% CI, 1.1 to 4.4) [31, 105]. Working women had 2.3 times the risk of developing preeclampsia compared with nonworking women [106]. Epidemiologic studies show that relative risk for preeclampsia is increased in many stressful situations [54, 107]. Many risk factors for preeclampsia are stress-related. Low-stress situations, on the contrary, are protective. Stress in pregnancy corroborates all physio-pathologic theories for preeclampsia [108].

Conclusion and Recommendation

Preeclampsia is a multifactorial disease. If greater awareness of the associated risk factors leads to earlier diagnosis and improved management,

there may be scope for reducing a proportion of the morbidity and mortality from preeclampsia. All the findings of the studies show the importance of gaining a comprehensive medical history from the women early in the pregnancy. Based on history, the screening should begin early to detect and treat the condition before it threatens the survival of mother and fetus.

The questions relating to family history of hypertension can be used as screening questions to identify pregnant women who need to be monitored more closely for the signs of preeclampsia during early pregnancy. On the basis of this review, future research is needed to formulate a predictable model for risk factors of PE to identify high risk women. Using the model specifically in developing countries, better screening for PE and monitoring of high risk women may lead to earlier diagnosis and improved management, thereby reducing a proportion of both maternal and fetal morbidity and mortality from PE.

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*All correspondences to: Dr. Uzma Shamsi, Department of Community Health Sciences, Aga Khan University Hospital, Stadium Road, Karachi-74800, Pakistan. E-mail ID: uzma.shamsi@aku.edu